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# Computed tomography predictors of hepatocellular carcinoma tumour necrosis after chemoembolization

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## Abstract

**Background:** Radiographical features associated with a favourable response to trans-arterial chemoembolization (TACE) are poorly defined for patients with hepatocellular carcinoma (HCC).

**Methods:** From 2008 to 2012, all first TACE interventions for HCC performed at the University of Alabama at Birmingham (UAB) were retrospectively reviewed. Only patients with a pre-TACE and a post-TACE computed tomography (CT) scan were included in the analyses ($n$ = 115). HCC tumour response to TACE was quantified via the the modified Response Evaluation Criteria in Solid Tumors (mRECIST) criteria. Univariate and multivariable analyses were constructed.

**Results:** The index HCC tumours experienced a > 90% or complete tumour necrosis in 59/115 (51%) of patients after the first TACE intervention. On univariate analysis, smaller tumour size, peripheral tumour location and arterial enhancement were associated with a > 90% or complete tumour necrosis, whereas, only smaller tumour size [odds ratio (OR) 0.62; 95% confidence interval (CI) 0.48, 0.81] and peripheral location (OR 6.91; 95% CI 1.75, 27.29) were significant on multivariable analysis. There was a trend towards improved survival in the patients that experienced a > 90% or complete tumour necrosis ($P$ = 0.08).

**Conclusions:** Peripherally located smaller HCC tumours are most likely to experience a > 90% or complete tumour necrosis after TACE. Surprisingly, arterial-phase enhancement and portal venous-phase washout were not significantly predictive of TACE-induced tumour necrosis. The TACE response was not statistically associated with improved survival.

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## Introduction

Trans-arterial chemoembolization (TACE) is a common oncological intervention in the treatment of hepatocellular carcinoma (HCC). There has been much debate over the efficacy of TACE prompting numerous survival studies with conflicting results. A commonly referenced meta-analysis of prospective randomized trials assessing TACE performed by Llovet *et al.* demonstrated a significantly improved 2-year survival compared with best supportive care.[1] These data have served as the basis of the American Association for the Study of Liver Disease (AASLD) practice guideline that 'TACE is recommended as first line non-curative therapy for non-surgical patients . . .'[2,3] Population-based data demonstrates that TACE is the most common oncological treatment performed for HCC in Medicare patients in the US.[4] Review of the Scientific Registry of Transplant Recipients (SRTR) data on liver transplantation for HCC also demonstrates that TACE is the most common bridging therapy offered to > 70% of waitlisted patients in the US.[5]

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Clinical studies have focused on the survival benefit of TACE with secondary outcomes being tumour necrosis quantified via the Response Evaluation Criteria for Solid Tumors (RECIST).[6] Studies demonstrate a correlation between HCC tumour response to TACE and survival.[7–9] However, there is little clinical data identifying pre-intervention cross-sectional radiographical tumour features that predict TACE-induced HCC tumour necrosis. The purpose of this study was to measure the association of pre-TACE computed tomography (CT) radiographical characteristics on post-TACE tumour necrosis. The primary endpoints for this study were modified (m)RECIST quantification of tumor necrosis and overall survival. Our hypotheses are (i) single tumours, smaller tumour size, peripheral tumour location, arterial-phase tumour enhancement and portal venous-phase tumour washout will be associated with a > 90% or complete HCC tumour necrosis, and (ii) patients with a > 90% or complete HCC tumour necrosis will experience improved survival compared with patients with < 90% tumour necrosis, stable or progressive disease.

## Methods

Ethics approval for this study was obtained from the University of Alabama Institutional Review Board (Protocol no. X100310006). A retrospective chart review was performed for all patients receiving a TACE at the University of Alabama at Birmingham (UAB) between January 2008 and June 2012. Patients were identified from an internal TACE database that is used for clinical purposes.

### Patient population

Patients were diagnosed with HCC by biopsy or by the presentation of classic HCC radiological features of a >2 cm hypervascular lesion arising in the setting of cirrhosis with arterial phase enhancement and portal venous phase washout.[10] The decision to offer TACE to patients with HCC was made by a multidisciplinary board at UAB including medical oncologists, surgeons, hepatologists and interventional radiologists. Candidacy for TACE was established using AASLD practice guidelines.[2,3] Select Child's B and Child's C cirrhotic patients were also offered TACE if they had an ECOG functional status of 0 or 1, had limited tumour burden and their decompensation symptoms were well controlled medically.

A list of all patients treated with TACE between January 2008 and June 2012 was generated from the UAB Interventional Radiology procedures electronic database. (Fig. 1) HCC tumours that had previously been treated with another loco-regional therapy such as radiofrequency ablation or external beam radiotherapy were excluded. Patients taking chemotherapeutic agents before and after the procedure were not excluded. HCC patients were only included if they had CT imaging within 75 days prior to the TACE procedure and follow-up imaging within 75 days after the TACE procedure.

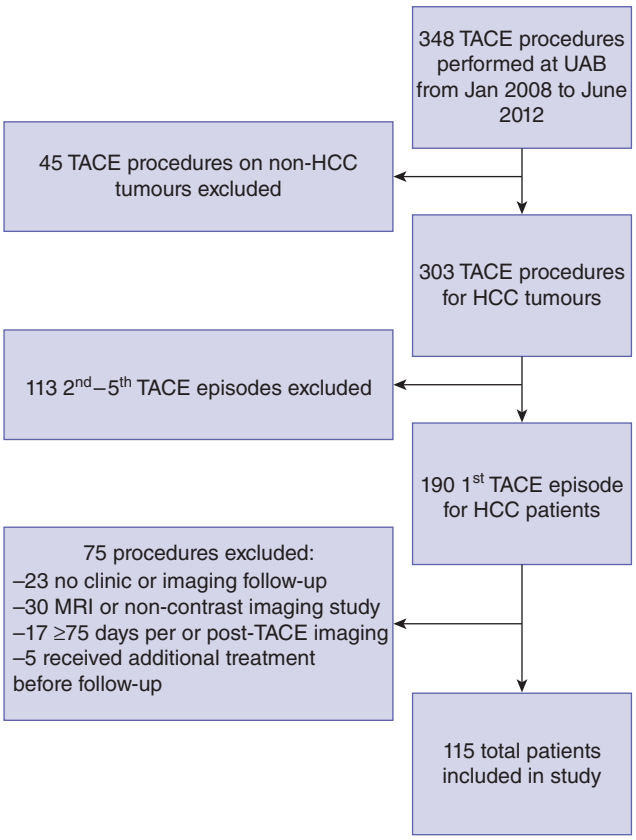


**Figure 1** Flow Diagram of 348 trans-arterial chemoembolization (TACE) procedures demonstrating the criteria used to select patients for this retrospective study

### CT technique

Three phase (unenhanced, arterial and portal venous phases) or four phase (unenhanced, arterial, portal venous and delayed phases) CT imaging were performed through the liver. All examinations were performed with a multi-detector row helical CT scanner with the following parameters: 120 kVp, 170–300 mAs (using automated dose modulation) and gantry rotation time of 0.5 s. The first phase was obtained without intravenous contrast. The contrast dose was calculated based on the patient's weight and renal function and was injected at a rate of 4 ml/s. The timing of the subsequent phases was based on bolus tracking which triggered when the region of interest (descending aorta) reached 150 HU. Multiphasic CT scans were then obtained at 15 s (arterial phase), 45 s (portal venous phase) and 3–5 min (delayed phase) post trigger.

### CT HCC tumour assessment and post-TACE mRECIST tumour necrosis quantification

After an extensive training period, two second year medical students (M.B. and D.D.) independently reviewed CT studies performed before and after TACE for all patients. The body radiology fellow (J.Z.) taught the medical students about the basics of mul-

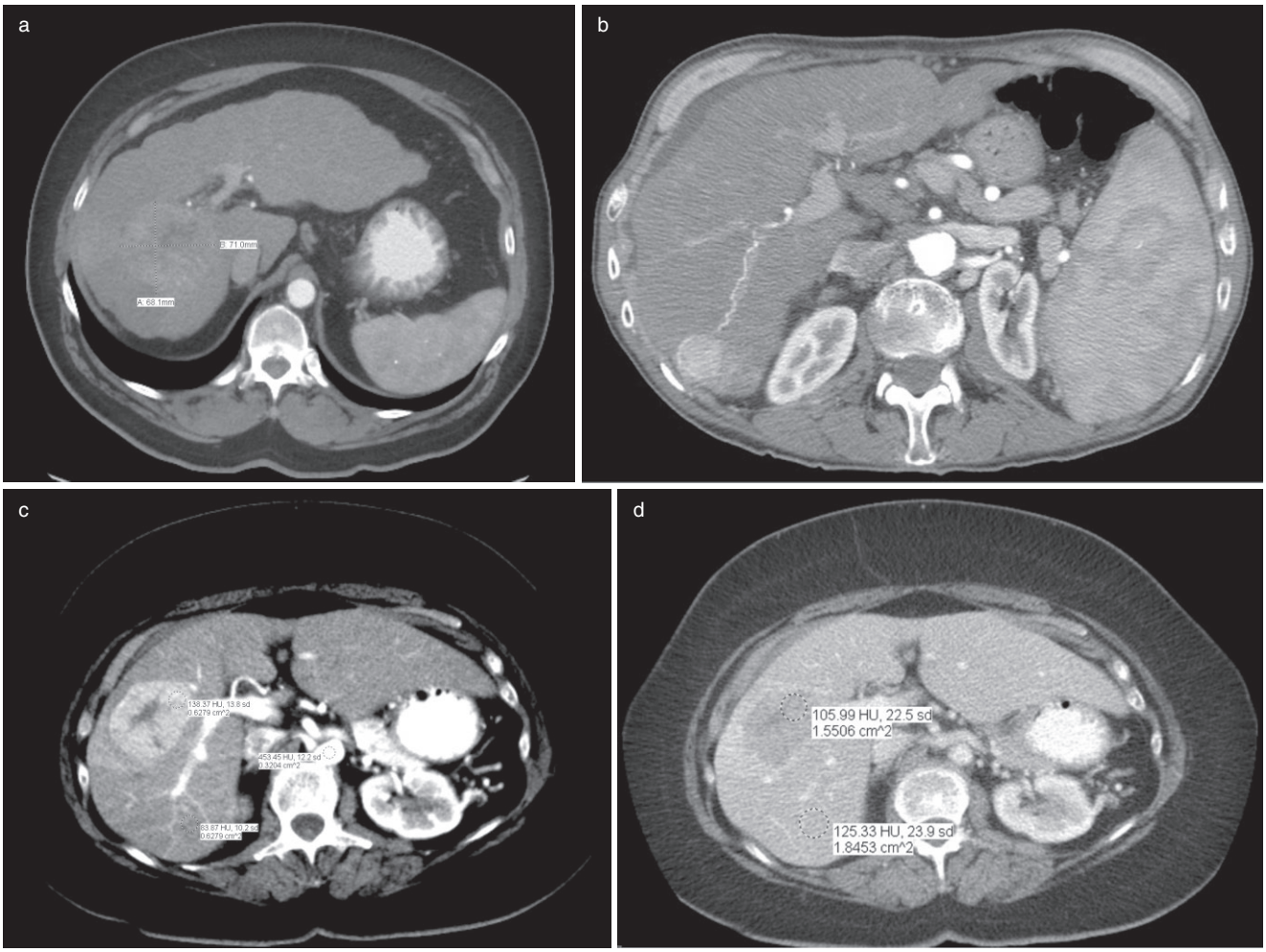


**Figure 2** (a) Axial computed tomography (CT) image demonstrating a central hepatocellular carcinoma (HCC) tumour. Central was defined as within 4 cm of portal vein bifurcation. (b) Axial CT image demonstrating a peripheral HCC tumour. Peripheral was defined as greater than 4 cm from portal bifurcation. Note also the presence of a clear feeding arterial vasculature. (c) Axial CT image demonstrating arterial phase tumour enhancement measurement. The arterial phase enhancement was measured as [Hounsfield units (HU) tumour-HU uninvolved liver]/HU aorta. The HU aorta was used to 'normalize' the measured enhancement to the variation observed in contrast bolus administration. (d) Axial CT image deomonstrating venous phase tumour washout measurement. The venous phase tumour washout was measured as (HU uninvolved liver – HU tumour). Efforts to 'normalize' this measurement to HU vena cava or HU aorta did not significantly alter the measurement and thus were not used

tiphasic CT and outlined a consistent approach to calculating axial tumour dimensions and measuring Hounsfield units. After these teaching sessions, the fellow and medical students jointly worked through 20 patients together. The medical students, body fellow and senior staff then reviewed 20 patients independently and the results were reviewed to verify consistency. The medical students then reviewed all CT imaging independently. The medical students saved the marked images indicating caliper and contrast enhancement measurements. The UAB CT body fellow (J.Z.) then independently reviewed all CT studies and confirmed all measurements. A staff radiologist (K.S.) with 19 years of experience confirmed all quantitative data.

The following baseline tumour characteristics were obtained from CT images prior to the procedure. Tumor size: consistent with mRECIST measurements, only axial imaging was used for tumour size measurements. Electronic calipers were used to measure the longest diameter of each tumour and the widest perpendicular measurement in the same image for use in calculating the cross-sectional tumour diameter. Tumour location: tumours were labelled central if within 4 cm of the portal vein bifurcation (Fig. 2a); all others were labelled peripheral (Fig. 2b). Both axial and coronal imaging was used to calculate the distance of the tumour from the portal vein bifurcation. Tumour enhancement: each reader measured the Hounsfield units (HU) of the

tumours in the unenhanced, arterial, portal venous and delayed (when available) phases. The arterial measurement was normalized to the enhancement in the aorta in the arterial phase (Fig. 2c). The portal venous washout measurement was normalized to the enhancement in the normal (uninvolved) liver parenchymal in the portal venous phase (Fig. 2d). Arterial enhancement was defined as [(tumor HU arterial phase – tumour HU pre-contrast phase)/HU aorta arterial phase)]. Portal venous washout was defined as (HU normal liver parenchyma Portal Venous Phase – HU Tumour Portal Venous Phase).

The tumour response was measured via the modified response evaluation criteria in solid tumours (mRECIST). In 2008, the AASLD modified the National Cancer Institute RECIST criteria to unify assessment of a radiographical response for hepatocellular carcinoma.[11] The modified RECIST criteria assess response based on residual arterial enhancement rather than purely tumour shrinkage measured by the greatest diameter of the lesion. Response data are presented for the largest lesion only, herein referred to as the index lesion. There are four categories of tumour response according to mRECIST: a complete response, partial response, stable disease or progressive disease.[11] A complete response is defined as the disappearance of tumour arterial enhancement. A partial response is defined as at least a 30% decrease in the diameter of arterial enhancement. For the purposes of the study, the partial response category was subdivided into a 60–90% and 30–60% response. Subcategorizing > 90% HCC necrosis is consistent with published literature evaluating angiographic predictors of TACE-induced tumour necrosis.[12] Stable disease is defined as a response that did not fall into the partial response or progressive disease category. Progressive disease is defined as growth of at least 20% of the sum of the longest diameter of the lesions.

### TACE protocol

The decision to offer TACE as loco-regional oncological therapy for patients with HCC was made at the UAB multidisciplinary liver tumour board. There were two general approaches to TACE. Single or oligo-HCC tumours, and all patients with compromised liver function, were generally treated with a Lipiodol-based TACE whereas multifocal HCC tumours were treated with drug-eluting beads (DEBS). Lipiodol-based TACE consisted of HCC embolization with a mixture of Lipiodol, 50 mg Doxorubicin and 400 μm Embozene® microspheres (CeloNova BioSciences, Inc., San Antonio, TX, USA). DEBS TACE consisted of either LC beads (Biocompatibles, Farnham, UK) or QuadraSpheres®-expanding microspheres (BioSphere Medical, Roissy-en-France, France). DEBS were eluted with 50 mg of Doxorubicin. In general, Lipiodol-based TACE was chosen for tumours that are potentially possible to treat with tumor-targeted embolization, leaving most of the non-tumour liver tissue unembolized, especially when the liver function is compromised. In contrast, non-tumour-targeted treatment with DEBS TACE was chosen for multifocal HCC tumours, although non-tumour-targeted treatment was only offered to patients with preserved liver function.

### Statistical analysis

Patient demographics, clinical history, laboratory data and CT imaging characteristics were collected. Patient and laboratory variables included age, gender, ethnicity, liver disease aetiology, alpha-fetoprotein, platelet count, model for end-stage liver disease (MELD) score and Child–Pugh Score. Patients taking Sorafenib chemotherapy within 90 days prior to or after the initial TACE were reported. General TACE data included TACE vehicle (Lipiodol or DEBS), repeat TACE within 6 months of initial TACE and total TACE procedures per patient. Pre-TACE imaging CT variables included tumour location (peripheral or central, right lobe versus not), the number of lesions, the size of tumours, the total diameter of the three largest tumours and HU measurements as described above. Data collected from post-TACE CT imaging include HCC tumour necrosis as measured according to mRECIST criteria.[11] To allow common statistical procedures, the analysis was restricted to examination of the index HCC tumour that was defined as the largest tumour (if more than one tumour per patient had been used in the analysis, the common assumption of independent data observations would have been violated). A two sample *t*-test was used to compare means between cohorts. The primary analytic approach for dichotomous variables utilized chi-square analyses. Logistic regression was used to predict response. Kaplan–Meier curves were constructed to evaluate patient survival. Survival probabilities were analysed with the log-rank test. For all inferences, the probability of a Type I error ($\alpha$) was set to 0.05. All analyses were conducted using the SAS 9.2 (SAS Inc., Cary, NC, USA).

## Results

### Patient cohorts: favourable response versus poor response to TACE

Between January 2008 and June 2012, 115 patients received a first TACE procedure for hepatocellular carcinoma at UAB . The HCC tumour necrosis distribution as measured by mRECIST is demonstrated in Fig. 3. Roughly half of the patients ($n$ = 59) had a complete or > 90% HCC tumour necrosis after TACE and are categorized as a favourable response. The remaining patients ($n$ = 56) had 60–90% or 30–60% tumour necrosis or stable disease or progressive disease and are categorized as a poor response.

### Patient and tumor demographics

The mean age of the TACE cohort was 62 years, 73% were male, 78% Caucasian and 92% were cirrhotic. There were no significant differences in age, gender, race, cirrhosis etiology, MELD score, Child's score or use of Sorafenib within 90 days pre- or post-TACE between the favourable response and poor response patients. (Table 1).

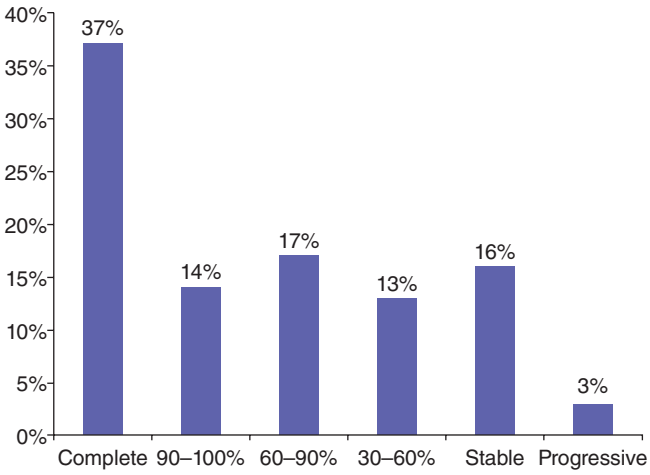


**Figure 3** Distribution of hepatocellular carcinoma (HCC) tumour necrosis after trans-arterial chemoembolization (TACE) as measured by modified response evaluation criteria in solid tumors (mRECIST) criteria. *Only data for index lesions are presented and considered for statistical analysis

### Tumour characteristics

AFP values were not significantly different between the favourable response and poor response groups. Radiographical data were recorded for 115 patients with over 210 lesions. The number of lesions per patient ranged from 1 to greater than 4. More than 4 lesions were appreciated in 16 patients. Fewer tumours were present in the patients that experienced a favourable response ($1.61 \pm 0.87$ versus $2.05 \pm 1.20$, $P = 0.0259$). The size of the largest tumour was smaller in the favourable response group ($3.7 \pm 1.7$ versus $5.7 \pm 3.5$, $P < 0.001$). Similarly, the total tumour diameter also was less in the favourable response group ($5.6 \pm 2.1$ versus $7.3 \pm 4.4$, $P < 0.0001$) (Table 2).

### TACE intervention

The use of lipiodol was much more common in the favourable response group compared with the poor response group (76.3% versus 44.6%, $P = 0005$). As expected, repeat TACE procedures within 6 months of the 'first' TACE procedure were less common in the favourable response group compared with the poor response group (23.7% versus 50.0%, $P = 0.0034$). There also was a trend towards fewer total TACE procedures done in the favourable response group compared with the poor response group, although this did not reach significance ($P = 0.09$) (Table 1).

### HCC tumour necrosis

Figure 4 demonstrates the differences in HCC tumour necrosis between a favourable response and poor response for the pre-TACE imaging variables. Peripherally located HCC lesions were more likely to have a favourable response compared with centrally located lesions [odds ratio (OR) 3.6 95% confidence interval (CI) 1.27, 11.87 $P = 0.015$]. A smaller maximal dimension of the HCC tumour was more likely to have a favourable response (OR 0.72 95% CI 0.58, 0.86 $P < 0.001$). Finally, HCC tumor arterial enhancement was also significantly associated with a favourable response to TACE (OR 1.05 95% CI 1.01, 1.10 $P = 0.046$). Neither clear feeding vasculature, tumour location in the right lobe versus other, a single HCC tumour versus multiple and portal vein washout were significantly associated with a favourable response to TACE on crude unadjusted analysis (Fig. 4, Table 3).

### Multivariable analysis of pre-TACE radiographical predictors of a favourable response to TACE

The multivariable analysis controlled for the TACE vehicle (lipiodol versus DEBS) because this variable was significantly different between the groups. Only smaller tumour size (OR 0.62 95% CI 0.48, 0.81 $P < 0.001$) and peripheral location (OR 6.91 95% CI 1.75, 27.29 $P = 0.006$) were significantly associated with a favourable response to TACE. Neither arterial enhancement or portal venous washout were associated with a > 90% or complete tumour necrosis in subgroup analyses of centrally located index HCC tumours <5 cm ($P$ = NS) or peripherally located HCC tumours <5 cm ($P$ = NS).

### Survival

Kaplan–Meier curves were constructed to measure the association between survival and TACE response. (Fig. 5) No deaths were appreciated for the first 3 months after the first TACE procedure. The survival curves converge briefly at 5–6 months, and then clearly separate. The crude unadjusted survival estimates were not significantly different between the groups ($P = 0.13$). After controlling for Child's score, there was a trend towards improved survival in the favourable response group although this did not reach statistical significance ($P = 0.08$).

## Discussion

Tumour characteristics obtained from cross-sectional liver imaging is utilized in patient selection for TACE. If characteristics predictive of complete or near complete HCC tumour necrosis could be identified on pre-therapy imaging, these parameters would be useful in selecting patients that may benefit from TACE. However, existing studies provide little conclusive evidence of a correlation between pre-TACE CT tumour imaging characteristics and a response to therapy. Instead, studies report predictive variables from TACE angiography and post-TACE imaging that is associated with HCC tumour necrosis. TACE angiography predictive factors include avid lesion enhancement on angiography during a TACE procedure,[12] the presence of a feeding artery >0.9 mm[12] and a concentration of lipiodol in the tumour.[12] Post-TACE imaging predictive factors include the absence of perfusion on post-TACE CT,[13] increased lipiodol retention[14,15] absence of portal vein thrombosis and arterioportal shunts,[16] a decrease in tumour size[12] and a lack of residual enhancement and a decrease in lesion size measured on post-TACE CT.[12] One of the shortcom-

**Table 1** Characteristics of patients with hepatocellular carcinoma treated with transarterial chemoembolization

| Cohort | Favourable response ($n$ = 59)[a] | Poor response ($n$ = 56)[a] | Significance |
|---|---|---|---|
| Age (years) | 61.7 ± 9.21 | 62.2 ± 11.7 | 0.79 |
| Male | 69.5% | 76.8% | 0.38 |
| Race: | | | |
| African American | 18.6% | 14.3% | 0.94 |
| White | 78.0% | 78.6% | |
| Other | 3.4% | 7.1% | |
| Aetiology:[b] | | | |
| HCV | 57.6% | 46.4% | 0.23 |
| NASH | 22.0% | 32.1% | 0.22 |
| Laennec's | 27.1% | 21.4% | 0.48 |
| HBV | 5.1% | 7.1% | 0.71 |
| Hemachromatosis | 3.4% | 1.8% | 1.00 |
| MELD Score | 11.0 ± 3.5 | 10.4 ± 3.2 | 0.33 |
| Child's Score: | | | |
| A | 47.5% | 58.9% | 0.22 |
| B | 49.2% | 37.7% | |
| C | 3.4% | 5.4% | |
| Evidence of portal HTN | | | 0.15 |
| Platelet < 100, cirrhosis | 50.9% | 51.8% | |
| Platelet > 100, cirrhosis | 45.8% | 35.7% | |
| Platelet > 100, no cirrhosis | 3.3% | 12.5% | |
| Sorafenib pre- or post-[c] | 28.8% | 39.3% | 0.24 |
| TACE vehicle | | | 0.0005 |
| Lipiodol | 76.3% | 44.6% | |
| Drug-eluting beads | 23.7% | 55.4% | |
| Repeat TACE within 6 months | 23.7% | 50.0% | 0.0034 |
| Total TACE procedures | | | 0.09 |
| 1 | 64.4% | 44.6% | |
| 2 | 28.8% | 41.1% | |
| 3 or more | 6.8% | 14.3% | |

AFP, alpha feto-protein; MELD, model for end-stage liver disease (range 6–40); NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; HTN, hypertension; TACE, transarterial chemoembolization.
[a]A favourable response is defined as complete or > 90% HCC tumour necrosis. A poor response is defined as < 90% HCC tumour necrosis, stable disease or disease progression. Tumour necrosis quantified via the modified response evaluation criteria in solid tumours criteria.
[b]Patients can have more than 1 aetiology of liver disease.
[c]Sorafenib use defined as within 90 day pre- or post-TACE.

ings of these studies is that the predictive factors are measured during or after the TACE procedure thus limiting the ability to use these data in pre-TACE patient selection.

The most important findings from this study are the identification of pre-TACE imaging HCC tumour characteristics that are predictive of tumour necrosis after TACE. We demonstrate that peripherally located and smaller HCC tumours identified on pre-TACE CT are more likely to experience complete or > 90% tumour necrosis after TACE. Centrally located tumours, defined as less than 4 cm from the portal vein bifurcation, had a very low rate of complete or > 90% tumour necrosis (5/22, 23%). The strongest predictive factor of a favourable response to TACE on multivariable analysis was the peripheral location (OR 6.91). As expected, smaller tumours were also more likely to experience a favourable response to TACE (OR 0.62/cm). The effect of tumour size was clearly demonstrated via the raw data where complete or > 90% tumour necrosis was observed in 20/30 (67%) tumours < 3 cm, 28/50 (56%) tumours 3–5 cm and 11/35 (31%) tumours >5 cm. Surprisingly, arterial enhancement was not significantly associated with HCC tumour necrosis on multivariable analysis,

**Table 2** Baseline hepatocellular carcinoma tumour characteristics

| | Favourable response ($n$ = 59)[a] | Poor response ($n$ = 56)[a] | Significance |
|---|---|---|---|
| Tumour number | 1.61 ± 0.87 | 2.05 ± 1.20 | 0.0259 |
| 1 | 57.6% | 46.5% | |
| 2 | 30.5% | 23.2% | |
| ≥3 | 11.9% | 21.4% | |
| Size of largest tumour | 3.7 ± 1.7 | 5.7 ± 3.5 | <0.001 |
| <3 cm | 33.9% | 17.9% | |
| 3–4.9 cm | 49.2% | 39.3% | |
| ≥5 cm | 16.9% | 42.8% | |
| Total tumour diameter[b] | 5.6 ± 2.1 | 7.3 ± 4.4 | 0.0001 |
| AFP level | | | |
| 1–15 | 46.0% | 48.9% | 0.19 |
| 16–500 | 44.0% | 28.8% | |
| >500 | 10.9% | 21.3% | |

cm, centimeters; AFP, alpha feto-protein; HCC, hepatocellular carcinoma.
[a]A favourable response is defined as complete or > 90% HCC tumour necrosis. A poor is response defined as <90% HCC tumour necrosis, stable disease or disease progression. Tumour necrosis quantified via the modified response evaluation criteria in solid tumours criteria.
[b]Total tumour diameter of the three largest lesions.

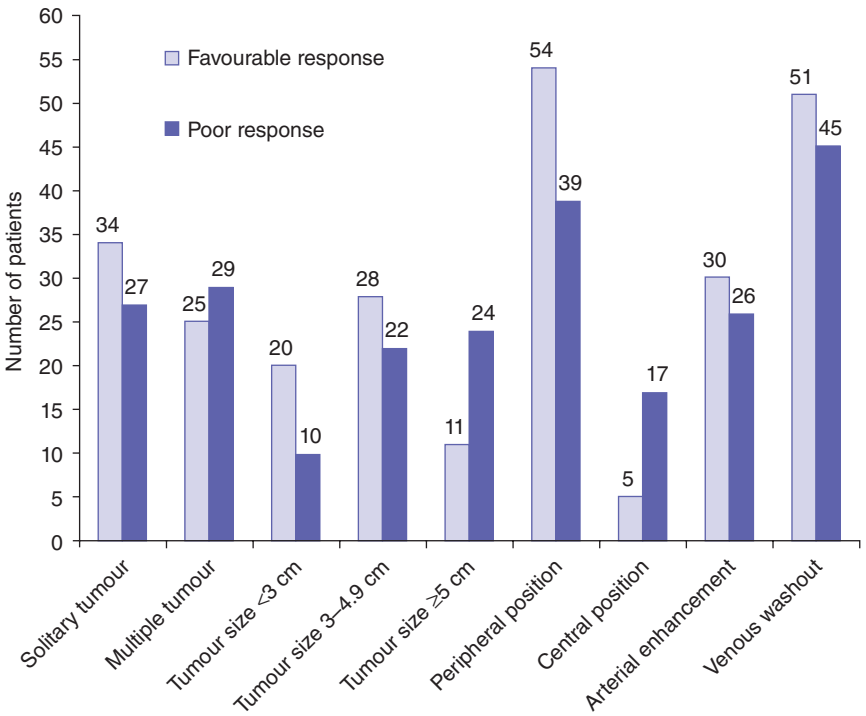


**Figure 4** Baseline hepatocellular carcinoma (HCC) tumour characteristics stratified by the response to trans-arterial chemoembolization (TACE). *A favourable response is defined as complete or > 90% HCC tumour necrosis. A poor response is defined as <90% HCC tumour necrosis, stable disease or disease progression. Tumour necrosis quantified via the modified response evaluation criteria in solid tumours criteria

in spite of the rational clinical perception that a HCC tumour that briskly enhances on CT-arterial phase should be more visible on TACE arteriogram and hence more likely to uptake embolic material and experience tumour necrosis.

Current recommendations for TACE for the oncological management of HCC have few tumour criteria.[2,3] This study is clinically important because tumour size and location, simply obtained from CT imaging, can be used to help clinicians decide whether or not to

**Table 3** Univariate versus multivariable analyses of pre-TACE CT imaging predictors of a > 90% or complete tumour necrosis as measured by mRECIST criteria

| | Univariate | | Multivariable | |
|---|---|---|---|---|
| | **Odds Ratio 95% CI** | ***P*-value** | **Odds Ratio 95% CI** | ***P*-value** |
| Peripheral HCC location[a] | 3.60 (1.27, 11.87) | 0.015 | 6.91 (1.75, 27.29) | 0.006 |
| Clear feeding vasculature | 0.95 (0.45, 1.99) | 0.881 | 1.12 (0.40, 3.12) | 0.832 |
| Lobe (right versus other) | 0.97 (0.41, 2.31) | 0.948 | 1.21 (0.39, 3.73) | 0.739 |
| Maximal tumour dimension | 0.72 (0.58, 0.86) | <0.001 | 0.62 (0.48, 0.81) | <0.001 |
| Single lesion | 1.57 (0.75, 3.30) | 0.231 | 1.46 (0.56, 3.84) | 0.441 |
| Arterial phase enhancement[b] | 1.05 (1.01, 1.10) | 0.046 | 1.03 (0.96, 1.09) | 0.441 |
| Portal venous washout[c] | 1.56 (0.58, 4.35) | 0.382 | 1.03 (0.26, 4.04) | 0.970 |

TACE, trans-arterial chemoembolization; CT, computed tomography; mRECIST, modified response evaluation criteria in solid tumours; HCC, hepatocellular carcinoma.
[a]Defined as > 4 cm from the portal vein bifurcation.
[b]Defined as [(Tumour HU Arterial Phase – Tumour HU Pre-Contrast Phase)/ HU Aorta Arterial Phase], where HU = Hounsfield Units.
[c]Defined as (HU Uninvolved Liver Parenchyma Portal Venous Phase – HU HCC Tumor Portal Venous Phase), where HU = Hounsfield Units.

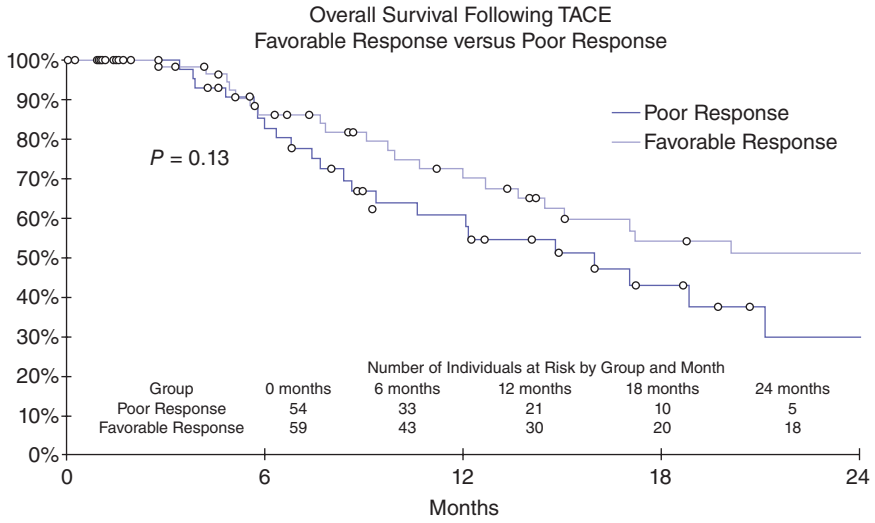


**Figure 5** Kaplan–Meier curve comparing overall survival in patients with a favourable response compared with a poor response to trans-arterial chemoembolization (TACE). Overall survival measured from the time of the first TACE procedure. *A favourable response is defined as complete or > 90% HCC tumour necrosis. A poor response is defined as < 90% HCC tumour necrosis, stable disease or disease progression. Tumour necrosis quantified via the modified response evaluation criteria in solid tumours criteria

offer TACE. For example, it may be reasonable to consider TACE even for patients with mild decompensation if the HCC tumour is small and peripherally located. A centrally located HCC tumour over 5 cm, in contrast, has a low likelihood of a favourable response to TACE and alternative treatment options may be considered.

There was a strong association between TACE vehicle and > 90% or complete HCC tumour necrosis. Clearly there is a selection bias contributing to this observation. We preferentially use Lipiodol for targeted embolization for single or oligo-HCC tumours and in all patients with compromised liver function. In contrast, DEBS was used for non-targeted multifocal HCC tumours. The selection bias in our clinical approach, however, only partially explains the very favourable results seen with Lipiodol. We plan to further investigate this observation with a larger patient cohort to enable controlling for tumour size, number and central versus peripheral location.

Fewer repeat TACE procedures were performed in the favourable response group within 6 months of the 'first' TACE. However, there was no statistically significant association between improved survival with TACE in the favourable response cohort on crude unadjusted analysis ($P = 0.13$). We adjusted the survival for Child's score because many of the Child's B and C patients where TACE was performed experienced a favourable outcome but their survival may be limited by underlying liver dysfunction. However, only a statistical trend emerged between survival and favourable response to TACE ($P = 0.08$) when controlling for Child's score. Examination of the Kaplan–Meier figure reveals that the post-TACE survival curves merge at 5–6 months and then separate.

From a statistical standpoint, survival curves that merge or cross cannot be significantly different thus explaining why seemingly divergent survival trajectories may not be statistically different. There are few studies in the literature examining the association between the response rate measured by mRECIST and overall survival after TACE. A randomized controlled trial by Llovet *et al.* found that response sustained at 6 months post-TACE correlated with improved survival.[17] Other studies show improved survival with a reduction in serum AFP after TACE,[18] multiple TACE procedures[8] and early-stage tumours.[19]

The main limitation of this study is its retrospective design and inherent practice patterns that may bias the data. For example, UAB has a more liberal policy for offering TACE to patients with liver dysfunction as long as the patient has a good functional status, no severe coagulopathy or medically refractory ascites. Over half of the favourable response group was Child's B or C cirrhotics, which undoubtedly leads to underestimation of TACE oncological survival advantage. In comparison, a previous meta-analysis proving the survival benefit of TACE included studies where Child's A patients accounted for 70–100% of reported cases.[1] The survival analysis was also limited by the small sample size raising the possibility of a type 2 statistical error. Another difference observed in our data is a higher objective radiographical response to TACE compared with most previous studies in the literature. Bruix *et al.* [20,21] summarized data from randomized prospective studies and reported a 15–55% TACE HCC tumour response whereas we observed an 81% response in this study.

In summary, we demonstrate that peripherally located and smaller HCC tumours identified on pre-TACE imaging are independent predictors of complete or >90 HCC tumour necrosis. These findings may be important in patient selection for TACE.

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### Conflicts of interest

None declared.

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